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PATENT
00961-P0213A SPM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re The Application Of	
Nicholas V. Perricone	Examiner: Simon J. Oh
Serial No.: 10/625,244	Group Art Unit: 1618
Filed: June 30, 2003	
For: Topical Benfotiamine Treatments	

Appeal Brief Under 37 CFR §41.37

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

A final rejection being mailed on June 28, 2006, and a Notice of Appeal having been filed on August 15, 2006, Appellant submits its Appeal Brief for the above-captioned application.

Certificate of Mailing: I hereby certify that this correspondence is today being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: : Mail Stop Appeal Brief – Patents; Commissioner for Patents; P.O. Box 1450; Alexandria, VA 22313-1450.

October 10, 2006

Stephen P. McNamara

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(i) Real Party in Interest

The real party in interest is N.V. Perricone, LLC, 639 Research Parkway, Meriden, Connecticut, 06450, the owner of the present application.

(ii) Related Appeals and Interferences

There are no related appeals or interferences.

(iii) Status Of Claims

Claims 10-18 and 21-26 are currently pending, stand rejected and are the subject of the instant Appeal. A copy of each of these claims is submitted in the attached Claims Appendix.

(iv) Status Of Amendments

There are no pending amendments to the claims. Applicant notes that claim 24 should be amended to insert --comprising-- after "A method for the reduction of glycation in cells of the skin".

(v) Summary of claimed subject matter

Independent Claim 10

Claim 10 relates to a method for the *reduction* of glycation in cells of the skin comprising: applying a composition containing an amount of benfotiamine effective to *reduce the quantity* of glycation proteins in said cells, in a dermatologically acceptable carrier, to skin tissue. (Specification, p. 4, lines 1-3, lines 11-12, lines 20-26; p. 4 , 1-16.)

Independent Claim 11

Claim 11 relates to a method for the *treatment* of glycation in cells of the skin comprising: applying a composition containing an amount of benfotiamine effective to *reduce the quantity* of glycation proteins in said cells, in a dermatologically acceptable carrier, to affected skin tissue. (Specification, p. 4, lines 1-3, lines 11-12, lines 20-26; p. 4 , 1-16.)

Independent Claim 12

Claim 12 relates to a method for the *treatment of damage* to the cells of the skin due to glycation comprising: applying a composition containing an amount of benfotiamine effective to *reduce formation* of glycation proteins in said cells, in a dermatologically acceptable carrier, to skin tissue. (Specification, p. 4, lines 1-3, lines 11-12, lines 20-26; p. 4 , 1-16.)

Independent Claim 13

Claim 13 relates to a method for the *treatment of aging* of the cells of the skin due to glycation comprising: applying a composition containing an amount of benfotiamine effective to *reduce formation* of glycation proteins in said cells, in a dermatologically acceptable carrier, to affected skin tissue. (Specification, p. 4, lines 1-3, lines 11-12, lines 20-26; p. 4 , 1-16.)

Independent Claim 21

Claim 21 relates to a method for the *treatment of glycation* in cells of the skin comprising: applying a composition containing an amount of *allithiamine* effective to reduce the quantity of glycation proteins in said cells, in a dermatologically acceptable carrier, to affected skin tissue. (Specification, p. 4, lines 1-3, lines 11-12, lines 20-26; p. 4 , 1-16.)

Independent Claim 22

Claim 22 relates to a method for the *treatment of aging* of the cells of the skin due to glycation, comprising: applying a composition containing an amount of *allithiamine* effective to reduce formation of glycation proteins in said cells, in a dermatologically acceptable carrier, to affected skin tissue. (Specification, p. 4, lines 1-3, lines 11-12, lines 20-26; p. 4 , 1-16.)

Independent Claim 24

Claim 24 relates to a method for the *reduction of glycation* of the cells of the skin due to glycation, comprising: applying a composition containing an amount of benfotiamine effective to *reduce formation* of glycation proteins in said cells, in a dermatologically acceptable carrier, to affected skin tissue.

Independent Claim 25

Claim 25 relates to a method for the *treatment of damage* of the cells of the skin due to glycation, comprising: applying a composition containing an amount of benfotiamine effective to *reduce the quantity* of glycation proteins in said cells, in a dermatologically acceptable carrier, to affected skin tissue.

Independent Claim 26

Claim 26 relates to a method for the *treatment of glycation* of the cells of the skin, comprising: applying a composition containing an amount of benfotiamine effective to *reduce formation* of glycation proteins in said cells, in a dermatologically acceptable carrier, to affected skin tissue.

(vi) Grounds of rejection to be reviewed upon appeal

Claims 10-18 and 21-26 stand rejected under 35 U.S.C. §103(a) as unpatentable over the combined disclosures of U.S. Patent 6,261,598 B1 to Runge and DE 4110087 to Woerwag.

(vii) Argument

Summary

The Examiner has claims 10-18 and 21-26 under 35 U.S.C. §103(a) as unpatentable over the combined disclosures of U.S. Patent 6,261,598 B1 to Runge and DE 4110087 to Woerwag.

Runge '598 discloses carotenoid formulations comprising a mixture of β-carotene, lycopene and lutein, and the use thereof in human and animal foods, cosmetics and pharmaceuticals.

Woerwag '087 discloses topical uses of benfotiamine for the treatment of rheumatism, joint and neurological problems.

The present invention is a treatment for the skin, addressing the symptoms of aging such as breakdown of collagen and loss of elasticity of the skin caused by the presence of glycated proteins in the skin (e.g. inflammation, wrinkles, brown spots, irritation and erythema). *See* Application ¶ [0009]. Once these glycated proteins are reduced and/or their formation prevented, the damaging effects on the skin are removed such that elasticity and a supple feeling is returned to the skin, fine lines and wrinkles are lightened, and skin coloring evens out. *See* Application ¶ [0010] (second occurrence).

Discussion of the Prior Art

Runge *et al.*, discloses oil dispersions of β-carotene, lycopene and lutein; which are Vitamin A derivatives. The most preferable compositions of the invention contain

greater than 98% of these active components. Benfotiamine is mentioned among a plethora of other possible ingredients which could be added to make up the remaining less than 2% of the composition. There is no discussion of the properties or effects of benfotiamine alone or when incorporated with any of these several other listed potential adjunct ingredients. There is no disclosure or suggestion to the method of the use of an effective amount of benfotiamine in a topical composition to improve skin condition, whereon the composition reduces or prevents formation of glycated proteins as is claimed by the Applicant. In fact, in the December 16, 2005 Office Action, the Examiner confirms that Runge does not explicitly teach methods of treating skin damage. *See* Office Action at p. 3. Hence Runge *et al.* does not teach or suggest the methods claimed in the present invention.

Woerwag et al. discloses treatment and amelioration of the nerve disorders including sciatica, neuritis, migraine, neuralgia, and shingles (a virus of the nerve cells) by topical treatment with benfotiamine. *See* Evidence Appendix, Woerwag Translation at col. 3, lines 50-57. The Examiner has cited the English-translated Abstract of Woerwag noting that it discloses benfotiamine compositions applied topically to the skin to treat disorders such as rheumatic disorders and shingles.

Grouping of the Claims of the Application

The claims of the present application present different aspects of the invention. These are grouped as follows:

(a) Treatment of aging in skin (claim 13, 22); and

(b) Prevention of glycation/glycated protiens in skin (claims 1, 12, 26); and

(c) Treatment/reduction of existing glycation/glycated protiens in skin (claims 11, 12, 21, 24, 25).

Patentability of the Claims

The patentability of each of these groups of claims should be analyzed separately, as follows:

Group (a) - claims 13 and 22, directed to treatment of *aging of skin cells*, is clearly not disclosed by or suggested by either of the cited references. The cited references are not at all relevant to these claims. The rejection of these claims should be reversed.

Group (b) – claims 12, 24, and 26 directed at methods of *prevention* of glycation is also not suggested or disclosed by either of the cited references. The cited references are not particularly relevant to these claims; and the rejection of these claims should also be reversed.

Group (c) – claims 10, 11, 21, 25, directed at methods of *treatment of/reduction of* existing glycation/glycated protien is the group of claims that the Examiner's rejection is relevant, even if misdirected.

As noted above, Woerwag et al. addresses treatment and amelioration of the nerve disorders including sciatica, neuritis, migraine, neuralgia, and shingles (a virus of the nerve cells). *See* Evidence Appendix, Woerwag Translation at col. 3, lines 50-57. Woerwag's compositions do not disclose topical application of benfotiamine to affect

the cells of the skin itself. Woerwag specifically teaches merely using the skin as a delivery vehicle, with the benfotiamine compositions passing there-through in order to acting upon the underlying internal body parts affected by disease/disorders such as the shingles virus. *See* Evidence Appendix, Woerwag translation at col. 3, lines 8-14. In particular, the Description of Woewarg discloses use of benfotiamine "locally to such area of the skin, which cover areas of the body that require treatment. " *See* Evidence Appendix, Woerwag Translation at col. 1, lines 53-55. Woerwag does not teach or suggest treatment of the skin cells directly, but rather acts upon the underlying body part and its cells to treat the disorder with which that body part is affected. As further stated in Woerwag:

> In all of these applications, benfotiamine, which is incorporated into ointment carriers, is applied to the appropriate skin area in the **region of the diseases body parts and can unfold its effect** very quickly in a targeted manner, usually after just a few minutes... *See id.* at col. 3, lines 57 to 62 (emphasis added).

Woerwag merely discloses delivery through-the-skin only in order to reach internal body parts for action upon the affected cells thereof, delivering benfotiamine therapy internally, and in alternate delivery form to the well-known oral therapies. In fact, Woerwag teaches away from directly acting upon and treating the cells of the skin, as it specifically discloses skin to merely be the "transportation path" used to reach the underlying body part that requires treatment. *See id* at. col. 2, lines 29-30. Thus in the preferred embodiment, Woerwag uses a liposome delivery system to deliver the substance to the desired target. Translation, Col. 2, line 55-Col. 3, line 19).

In contrast, all claims of the present invention requires compositions acting directly upon the cells of skin. See independent claims 10-13, 21-22, 24-26, as amended herein). Further, claims of the present invention require that upon acting directly upon the cells of the skin, the composition reduces the quantity of glycated proteins (claims 10, 11, 13, 21, and 25) or reduces the formation of glycated proteins (claims 12, 22, 24, and 26).

Further, if the benfotiamine composition of Woerwag were modified to act upon and treated the cells of the skin directly, it would frustrate the explicitly disclosed purpose of Woerwag, i.e, to pass through the skin to deliver benfotiamine to the underlying body part and the cells thereof to treat the disease/disorder, and thus, would render Woerwag non-functioning and inoperative in treating the underlying body part requiring treatment. Hence, there would be no suggestion or motivation to modify Woerwag to have its compositions alternatively act upon the cells of the skin.

Runge and Woerwag do not teach or suggest benfotiamine for action directly upon the cells of the skin, never-mind improvement of skin, wherein the composition reduces the quantity of glycated proteins (claims 10, 11, 13, 21, and 25) or reduces the formation of glycated proteins (claims 12, 22, 24, and 26) as is presently claimed. Hence, for at least these reasons, Applicant's present claims are patentable over Runge in view of Woerwag.

The Examiner states that there exists an overlap in the patient populations between those that would likely be treated by the presently claimed methods and those of Woerwag suffering from rheumatic disorders and shingles, who are more likely to be

middle-aged to elderly. Applicant respectfully disagrees, as the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) states that rheumatic disorders affect people of all ages, as is true of the many other listed diseases in Woerwag. *See* National Institutes of Health (NIH) Publication No. 02-4999. A population of individuals who are dealing with a chronic condition or disease, looking to internal treatment of benfotiamine as a treatment is quite different from the population who are dealing with the normal effects of aging, such as wrinkles, break down of collagen and loss of elasticity of the skin, looking to improve their appearance. These populations are experiencing substantially different conditions, are looking for very different benefits, and do not overlap in this sense.

Conclusion

The cited references, individually or in combination, do not disclose or suggest the claimed methods to (a) treat aging; (b) prevent glycation of skin cells; or (c) treat glycation of skin cells.

The claimed invention would not have been obvious to a person of ordinary skill in the art at the time of the invention thereof. Accordingly, for all of the foregoing reasons, the rejection of claims 1-18 and 21-26 should be reversed, and it is respectfully requested that the Examiner be directed to issue a Notice of Allowance of claims 1-18 and 21-26.

Respectfully submitted,

October 10, 2006

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Attorneys for Appellant

(viii) Claims appendix

1-9. Cancelled

10. A method for the reduction of glycation in cells of the skin comprising: applying a composition acting directly upon said skin cells containing an amount of benfotiamine effective to reduce the quantity of glycated proteins in said skin cells, in a dermatologically acceptable carrier, to skin tissue.

11. A method for the treatment of glycation in cells of the skin comprising: applying a composition acting directly upon said skin cells containing an amount of benfotiamine effective to reduce the quantity of glycated proteins in said skin cells, in a dermatologically acceptable carrier, to affected skin tissue.

12. A method for the treatment of damage to the cells of the skin due to glycation comprising: applying a composition acting directly upon said skin cells containing an amount of benfotiamine effective to reduce formation of glycated proteins in said cells, in a dermatologically acceptable carrier, to skin tissue.

13. A method for the treatment of aging of the cells of the skin due to glycation comprising: applying a composition acting directly upon said skin cells containing an amount of benfotiamine effective to reduce quantity of glycated proteins in said cells, in a dermatologically acceptable carrier, to affected skin tissue.

14. A method in accordance with claims 10, 11, 12, or 13 wherein said composition further comprises one or more additional ingredients selected from the group consisting of: ascorbic acid and ascorbic acid derivatives; lipoic acid; α-hydroxy acids; and tocotrienols and tocotrienol derivatives and vitamin E compositions enriched with tocotrienols or tocotrienol derivatives.

15. A method in accordance with claims 10, 11, 12, or 13, wherein the composition contains from about .05% to about 70% by weight benfotiamine.

16. A method in accordance with claim 15, wherein the composition contains from about 5% to about 20% by weight benfotiamine.

17. A method in accordance with claim 15, wherein the composition contains from about .05% to about 5% by weight benfotiamine.

18. A method in accordance with claim 15, wherein the composition contains from about .25% to about 7% by weight benfotiamine.

19-20. Cancelled

21. A method for the treatment of glycation in the cells of the skin comprising: applying a composition acting directly upon said skin cells containing an amount of allithiamine effective to reduce the quantity of glycated proteins in said cells, in a dermatologically acceptable carrier, to affected skin tissue.

22. A method for the treatment of aging of the cells of the skin due to glycation, comprising: applying a composition acting directly upon said skin cells containing an amount of allithiamine effective to reduce formation of glycated proteins in said cells, in a dermatologically acceptable carrier, to affected skin tissue.

23. A method in accordance with claims 21 or 22, wherein the allithiamine consists of benfotiamine.

24. A method for the reduction of glycation in cells of the skin: applying a composition acting directly upon said skin cells containing an amount of benfotiamine effective to reduce formation of glycated proteins in said cells, in a dermatologically acceptable carrier, to affected skin tissue.

25. A method for the treatment of damage to the cells of the skin due to glycation comprising: applying a composition acting directly upon said skin cells containing an amount of benfotiamine effective to reduce quantity of glycated proteins in said cells, in a dermatologically acceptable carrier, to affected skin tissue.

26. A method for the treatment of glycation in the cells of the skin comprising: applying

a composition acting directly upon said skin cells containing an amount of benfotiamine effective to reduce formation of glycated proteins in said cells, in a dermatologically acceptable carrier, to affected skin tissue.

(ix) Evidence appendix

Translation of the Specification of Woerwag, DE 41 10 087 A

Description

The invention relates to a pharmaceutical containing Benfotiamin and to its use.

Benfotiamin (S-benzoylthiamine-O-monophosphate) is a lipid-soluble form of vitamin B1. The symptoms of vitamin B1 deficiency are lack of appetite, vomiting, resorption disorders, fatigue, paralysis and mental changes such as loss of memory, confusion and depression. These deficiencies are known as Beri-Beri disease. Vitamin B1, a water-soluble vitamin, is therefore not a suitable pharmaceutical for treating these states of vitamin B1 deficiency because it has limited bioavailability (only about 5% of an oral administration is resorbed) and has retention properties. For this reason, vitamin B1 may have to be administered in very high doses.

It is already known to administer the lipid-soluble form of vitamin B1, namely Benfotiamin, in the form of coated tablets in order to achieve improved resorption in the intestinal tract compared to the water-soluble vitamin B1. Benfotiamin is cleaved upon absorption in the cell system and the active ingredient, namely thiamine, is released.

The disadvantage of the familiar application method is that a localized application is not possible due to the oral administration. Consequently, the dose to be administered must be so high that the site, from which for example a vitamin B1 deficiency is supposed to be eliminated or at which a therapeutically necessary concentration is supposed to be present, must contain sufficient Benfotiamin that it can be cleaved into the active ingredient thiamine (vitamin B1). If for example a painful inflammation of a foot joint caused by vitamin B1 deficiency is supposed to be treated, a sufficient quantity of Benfotiamin has to be administered to ensure that following the resorption in the intestinal tract enough Benfotiamin is present at the site to be treated, which is then cleaved into thiamine and available as the active ingredient. During this process, the organism of course transports the resorbed Benfotiamin not only to this site, but distributes it throughout the entire organism. As a result, the Benfotiamin is also cleaved in cells with no vitamin B1 deficiency, releasing thiamine, although this is not required in these cells. An increased vitamin B1 supply to the body expresses itself in an extremely unpleasant body odor.

It is the object of the present invention to overcome these disadvantages and create a pharmaceutical of the type mentioned above, which can be applied locally.

According to the invention, the object is achieved with a pharmaceutical, in which Benfotiamin is taken up and distributed throughout a carrier and which is applied topically to the skin.

If a carrier takes up Benfotiamin, the resulting ointment or cream can be applied for example locally to such areas of the skin, which cover the areas of the body that require treatment. The carrier ensures that the Benfotiamin stays in that location and offers the possibility of Benfotiamin penetrating through the skin into the cell system beneath. Dephosphorylation into S-benzoylthiamine (SBT) then occurs in the cell system as a result of phosphatases inherent to the cells. Thereafter, SBT is converted into thiamine by means of enzymatic debenzoylation, which thiamine in turn is converted into cocarboxylase with metabolic activity.

It was found that the lack of sufficient quantities of cocarboxylase in diseased sites results in an accumulation of intermediary decomposition products such as pyruvate, lactate and ketoglutarate. This leads to inflammations, which are associated with pain. Following its penetration through the skin and conversion into cocarboxylase, Benfotiamin inhibits the accumulation of these toxic matters. Studies have shown that an antinociceptive effect is achieved, i.e. thiamine occupies pain receptors and consequently inhibits the transmission of the pain sensation.

Introducing Benfotiamin into the carrier opens up the possibility of applying Benfotiamin through targeted local action via the skin into the areas of the body requiring treatment, where it is then converted into the active ingredient thiamine and/or cocarboxylase. The advantages are not only that a localized application becomes possible, but also that due to the particular penetration mechanism and the subsequent release of thiamine a significantly more rapid administration of the active ingredient to the site to be treated is achieved. Additionally, it is possible to use considerably less Benfotiamin on an overall basis compared to the administration in the form of coated tablets, because only a relatively small portion of Benfotiamin is already converted into thiamine on the relatively short transportation path between the skin and the treated body areas before reaching the cell regions that in fact require treatment. The conversion mechanism of Benfotiamin into thiamine is carried out in the cells regardless of whether a disease pattern exists or not, i.e. in the case of oral administration such a conversion takes place directly following absorption in the cell system of the gastrointestinal tract. As a result, it must be ensured that the amount of Benfotiamin at the treatment site is still sufficient so that it can be converted on site into the active ingredients thiamine and/or cocarboxylase. These disadvantages are overcome with the topical external application, and also the effects of unpleasant body odor associated with a high dose of vitamin B1 are eliminated. The topical analgesic and antiphlogistic effects achieved with the external administration according to the invention can be achieved quickly, lastingly, within a targeted local area and, unlike oral administration, with significantly lower quantities of Benfotiamin.

In another embodiment of the invention, the carrier is a lipophilic carrier in ointment form.

This measure has the advantage that the pharmaceutical has the form of an ointment or a cream, which is easy to handle and can be applied with good adhesion on the human skin or be massaged into it. Benfotiamin can be distributed in the lipophilic carrier matrix for example as a finely dispersed solid matter. Massaging the ointment- or cream-like carrier into the skin shortens the penetration phase.

In a special embodiment of the invention, the carrier contains liposomes, in the aqueous interior of which the Benfotiamin can be found.

Liposomes are spherical shapes made of one or more concentrated lipid bilayers with aqueous interior. Vesicles like these can be produced by finely distributing – mechanically - the phospholipids (e.g. lecithin) in aqueous

media. The measure suggested here, namely to introduce the Benfotiamin in the aqueous phase in the inside of the liposomes, offers the considerable advantage that the Benfotiamin can be taken up in the lipophilic carrier relatively safely and protected from external influence. Furthermore this measures has the considerable advantage that the liposomes penetrate very quickly through the skin areas and release Benfotiamin only in the body's cells beneath the skin. This way, quick, targeted administration of the Benfotiamin into the areas of the body requiring treatment can be achieved. Upon release of Benfotiamin, the previously described conversion mechanism in the cells can take place and convert it into thiamine and cocarboxylase. This measure now offers the additional considerable advantage that Benfotiamin can be supplied to the body regions requiring treatment nearly completely, undecomposed, and encapsulated in the liposomes.

As a result, extremely rapid and targeted treatment is possible, using relatively small amounts of the active ingredient.

In another embodiment of the invention, the carrier is a lipophobic carrier containing detergents, which effect a distribution of Benfotiamin in the lipophobic phase.

This measure has the advantage that Benfotiamin can be taken up in a lipophobic carrier via detergents, which are known per se, so that the pharmaceutical approximately has the consistency of a fluid, which can be distributed very quickly and evenly if it needs to be applied across a large area. To this end, the lipophobic carriers can be such that they largely evaporate as soon as they are applied on the skin, forming a film-like layer on the skin. This is desirable, for example, when the skin areas are supposed to be covered by clothing immediately following the application of the pharmaceutical, without the clothing sticking to the treated skin areas and causing inconvenience.

In another embodiment of the invention, the pharmaceutical is applied in the form of an aerosol.

This measure has the advantage that the pharmaceutical can be applied quickly and easily on the skin. The Benfotiamin can be present as a suspension in a liquefied gas under pressure as the propellant and be applied to the body as the propellant is released as a finely dispersed solid matter. It is also conceivable to include Benfotiamin in a lipophilic or lipophobic phase in the propellant, so that the carrier along with Benfotiamin is applied onto the skin as a finely dispersed film-like coating after the aerosol comes in contact with the skin.

Studies have shown that a pharmaceutical of this type can be used to treat the following diseases: rheumatic disorders; general joint and muscle pain, irritated radicular syndrome of the spinal cord, cervical syndrome, shoulder-arm syndrome, symptoms resulting from polyarthritis, tennis elbow, stiff neck, lumbago, sciatic pain syndrome, intervertebral disk problems, arthrosis, polyneuropathy, neuritis, migraine, neuralgia, shingles and facial paralysis.

In all these applications, Benfotiamin, which is incorporated in ointment carriers, is applied to the appropriate skin area in the region of the diseases body parts and can unfold its effect very quickly and in a targeted manner, usually after just a few minutes.

The afore-mentioned characteristics and those explained below can of course be used not only in the described combination, but also in other combinations or alone, without departing from the idea of the present invention.

The invention will be explained more closely hereinafter with reference to a few select embodiments:

Example 1

5.0 g Benfotiamin is introduced in the familiar manner into 95.0 g unguentum emulsificans.

The resultant ointment is massaged into the skin, and a significant relief of pain was noticed following just a few minutes for the following disease patterns: rheumatic pain, general joint and muscle pain, irritated radicular syndrome of the spinal column, cervical syndrome, shoulder-arm syndrome, symptoms resulting from polyarthritis, tennis elbow, stiff neck, lumbago, sciatic pain syndrome, intervertebral disk problems, arthrosis, polyneuropathy, neuritis, migraine, neuralgia, shingles and facial paralysis.

Example 2

An aqueous saturated solution of Benfotiamin is prepared, wherein the aqueous phase is adjusted to a pH of 8 for better solubility.

Then the aqueous phase is mixed with lecithin, and while stirring vigorously and at the same time applying pressure surges on the liquid an emulsion is prepared, containing spherical structures measuring between 25 nm and 1 µm in diameter. The spherical liposomes enclose an aqueous phase, which contains the Benfotiamin. Depending on the quantity of lecithin that is added, a more ointment-like or a more cream-like emulsion is obtained.

The resultant emulsion is massaged into the appropriate areas of the skin, as described in Example 1, wherein the disease patterns were the same as those outlined in Example 1.

In all cases, consistently even faster effects were achieved.

TRANSLATOR CERTIFICATION

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Morningside | Translations

I, Kerstin Roland, a translator fluent in the German language, on behalf of Morningside Evaluations and Consulting, do solemnly and sincerely declare that the following is, to the best of my knowledge and belief, a true and correct translation of the document(s) listed below in a form that best reflects the intention and meaning of the original text.

MORNINGSIDE EVALUATIONS AND CONSULTING

Kerstin Roland

Signature of Translator

Description of Documents Translated:
DE 41 10 087 A1: Pharmaceutical containing Benfotiamin and its use

Date: March 24, 2006

(x) Related proceedings appendix

None

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